# Predictive Factors to Guide Individualized Stimulation with rec-FSH

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After introduction of the rFSH preparations, lower presentation forms were available and patient friendly presentation forms for optimal flexibility and patient individualisation, such as the Puregon® Pen have been developed. However, the optimal starting dose of rFSH during the first treatment cycle in IVF and ICSI remains controversial. The majority of fertility clinics have chosen a "standard dose" for "standard patient". A number of studies have attempted to define an optimal standard dose. It varies between 100 and 250 IU/day, reflecting the range of policies from "friendly IVF" with a minimal dose, to an approach where a large number of oocytes is considered a criteria of success. The problem is that "standard patients" treated with "standard doses" frequently do not exhibit "standard responses". The question is how, and to what extent, it is possible to avoid the inappropriate responses by adjusting the dose of rFSH. They may be due to inherent biological mechanisms in relation to differences in the number of recruitable follicles, follicle sensitivity to rFSH and pharmacodynamics. On the other hand they may also be due to factors that may be predicted and at least partly controlled.

A "standard patient" is below 40 years of age with a normal serum FSH, regular and ovulatory menstrual cycle and a normal body weight. The difficult clinical decision is the dose to be used for the 1st week during the 1st treatment cycle, where the ovarian response to FSH is basically unknown. From day 8 onwards the response is often evident and adjustments can be made. We have looked at this through a retrospective study on the impact of dose adjustments and through a prospective trial on response prediction.

## 1. Retrospective Study

The study included 251 "standard" patients treated with a "standard" rFSH dose of 150 IU/day who failed to achieve pregnancy during the 1st treatment cycle and were subsequently treated with a 2nd cycle. In the 2nd cycle the rFSH starting dose was adjusted according to the response in the 1st cycle. The impact of FSH dose adjustments on the number and distribution of oocytes in the two cycles was assessed. Alterations of the starting dose (mean increase by 87 units/day or decrease by 50 units/day) caused a significant ($p<0.05$) increase (by 1.5) or decrease (by 1.4) of the number of oocytes. Our conclusion is that among "standard" patients treated with the "standard" rFSH dose of 150 IU/day more than 50% of patients needed a dose adjustment in the subsequent cycle.

## 2. Prospective Response Prediction Study

**Methods**

This trial included 156 "standard patients" treated for the 1st treatment cycle with 150 IU/day of rFSH (Puregon®, NV Organon, Oss, The Netherlands). Down regulation was achieved using the long protocol starting on day 21. 145 patients could be evaluated. The purpose of this study was to identify those independent factors that predict the ovarian response through a multiple regression analysis and construct a rFSH dosage score which is a dosage normogram based on independent variables. The following variables were examined as possible predictive factors:

- age, weight, body mass index, cycle length, smoking status
- on day 2-5, total ovarian volume, total number of small follicles (<5 mm and 5~10 mm in diameter), doppler of the ovarian blood flow and hormonal markers (FSH, oestradiol, testosterone and inhibin B).

The primary end points were the number of aspirated follicles and oocytes retrieved.

**Results**

When multiple regression analysis was performed with the number of follicles aspirated as the dependent variable the following model was obtained:

Number of follicles aspirated = -8.485 + 0.06468 x BMI + 2.074 x smoking status + 0.383 x total number of small follicles + 1.625 x total doppler score + 2.670 x serum testosterone

Multiple regression was also performed with the number of oocytes as the dependent variable and the following model was obtained:

Number of oocytes = 6.509 − 0.307x age + 0.06548 x BMI + 0.227 x total number of small follicles + 1.716 x total doppler score

Ovarian volume significantly correlated to both the number of follicles and the number of oocytes ($p<.000$) in linear regression, but was not an independent variable.

**Conclusion**

Body mass index (BMI), smoking status, total number of small follicles, total doppler score and serum testosterone proved to predict the number of follicles aspirated while age, BMI, total number of small follicles and total doppler score predicted the number of oocytes retrieved.

The construction of the rFSH dosage normogram should be based on these scientifically proven independent predictors. However, clinical experience and safety considerations must be taken into account. Suggestions for different rFSH dosage normograms for clinical testing are currently being constructed and will be presented at the meeting.